

PATENT  
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Masafumi FUKAE et al.

Serial No.: Not Yet Assigned  
(§371 international application No. PCT/JP01/04059)

Filed: January 9, 2002

For: METHODS FOR CRYSTALLIZATION OF N- (1 (S) -ETHOXYCARBONYL-3-PHENYLPROPYL) -L-ALANINE N-CARBOXYANHYDRIDE

PRELIMINARY AMENDMENT

Commissioner for Patents  
Washington, D.C. 20231

January 9, 2002

Sir:

Prior to the calculation of the filing fees of the above application, please amend the application as follows:

IN THE CLAIMS:

Please amend the following claims as follows:

9. (Amended) The crystallization method according to Claim 1

wherein the good solvent is a hydrogenated hydrocarbon, an ether, a nitrile, an ester, a ketone or a mixed solvent thereof.

16. (Amended) The crystallization method according to Claim 1

wherein the addition of the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent is carried out by a sequential addition.

18. (Amended) The crystallization method according to any one of Claims 1 to 4

wherein the addition of the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent to the aliphatic hydrocarbon solvent is carried out in a condition that a crystal of said N-carboxylic anhydride is added to said aliphatic hydrocarbon solvent in advance.

20. (Amended) The crystallization method according to any one of Claims 1 to 4

wherein the addition of the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent to the aliphatic hydrocarbon solvent is carried out by adding a portion of said solution in the good solvent to said aliphatic hydrocarbon solvent in advance to thereby prepare a slurry in which said N-carboxylic anhydride is precipitated, followed by adding the rest of said solution in a good solvent to said slurry.

22. (Amended) The crystallization method according to any one of Claims 1 to 4

wherein an amount of a precipitated crystal is increased by adjusting a liquid temperature to -30 to 25°C following completion of the addition.

23. (Amended) The crystallization method according to any one of Claims 1 to 4

wherein a weight ratio of the good solvent to the aliphatic hydrocarbon solvent at completion of the addition is 0.001 to 1.

25. (Amended) The crystallization method according to any one of Claims 1 to 4

wherein the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent is

an NCA forming reaction solution obtained by reacting N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine with N,N'-carbonyldiimidazole or phosgene or

a solution obtained by subjecting the reaction solution to concentration or solvent exchange.

27. (Amended) The crystallization method according to Claim 25

wherein an NCA forming reaction solvent doubles as the good solvent for the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent.

35. (Amended) The crystallization method according to any one of Claims 28 to 30

wherein the good solvent is a halogenated hydrocarbon, an ether, a nitrile, an ester, a ketone or a mixed solvent thereof.

42. (Amended) The crystallization method according to any one of Claims 28 to 30

wherein the addition of the aliphatic hydrocarbon solvent to the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent is carried out under stirring with a stirring force corresponding to a stirring power requirement of not less than 0.1 kW/m<sup>3</sup>.

44. (Amended) The crystallization method according to any one of Claims 28 to 30

wherein the addition of the aliphatic hydrocarbon solvent to the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)- L-alanine N-carboxylic anhydride in the good solvent is carried out by preparing a slurry of said N-carboxylic anhydride in advance and adding the aliphatic hydrocarbon solvent sequentially to said slurry.

46. (Amended) The crystallization method according to Claim 44

wherein the preparation of the slurry is carried out by sequential addition of the aliphatic hydrocarbon solvent to the solution of said N-carboxylic anhydride in the good solvent and/or by addition of a crystal of said N-carboxylic anhydride to the solution of said N-carboxylic anhydride in the good solvent.

48. (Amended) The crystallization method according to any one of Claims 28 to 30

wherein the weight ratio of the good solvent to the aliphatic hydrocarbon solvent is 0.001 to 1 at completion of the addition.

50. (Amended) The crystallization method according to any one of Claims 28 to 30

wherein an amount of a precipitated crystal is increased by adjusting a liquid temperature to -30 to 25 following completion of the addition.

51. (Amended) The crystallization method according to any one of Claims 28 to 30

wherein the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent is

an NCA forming reaction solution obtained by reacting N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine with N,N'-carbonyldiimidazole or phosgene or a solution obtained by subjecting the reaction solution to concentration or solvent exchange.

53. (Amended) The crystallization method according to Claim 51

wherein an NCA forming reaction solvent doubles as the good solvent for the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent.

REMARKS


The above amendment is believed to place the claims in proper condition for examination.  
Early and favorable action is awaited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

In the event there are any additional fees required, please charge our Deposit Account No. 01-2340.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

The following claims have been amended as follows:

9. (Amended) The crystallization method according to ~~any one of Claims 1 to 8~~ Claim 1 wherein the good solvent is a hydrogenated hydrocarbon, an ether, a nitrile, an ester, a ketone or a mixed solvent thereof.

16. (Amended) The crystallization method according to ~~any one of Claims 1 to 15~~ Claim 1 wherein the addition of the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent is carried out by a sequential addition.

18. (Amended) The crystallization method according to any one of Claims 1 to ~~17~~ 4 wherein the addition of the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent to the aliphatic hydrocarbon solvent is carried out in a condition that a crystal of said N-carboxylic anhydride is added to said aliphatic hydrocarbon solvent in advance.

20. (Amended) The crystallization method according to any one of Claims 1 to ~~19~~ 4 wherein the addition of the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent to the aliphatic hydrocarbon solvent is carried out by adding a portion of said solution in the good solvent to said aliphatic hydrocarbon solvent in advance

to thereby prepare a slurry in which said N-carboxylic anhydride is precipitated, followed by adding the rest of said solution in a good solvent to said slurry.

22. (Amended) The crystallization method according to any one of Claims 1 to ~~21~~ 4 wherein an amount of a precipitated crystal is increased by adjusting a liquid temperature to -30 to 25°C following completion of the addition.

23. (Amended) The crystallization method according to any one of Claims 1 to ~~22~~ 4 wherein a weight ratio of the good solvent to the aliphatic hydrocarbon solvent at completion of the addition is 0.001 to 1.

25. (Amended) The crystallization method according to any one of Claims 1 to ~~24~~ 4 wherein the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent is an NCA forming reaction solution obtained by reacting N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine with N,N'-carbonyldiimidazole or phosgene or a solution obtained by subjecting the reaction solution to concentration or solvent exchange.

27. (Amended) The crystallization method according to Claim 25 ~~or 26~~ wherein an NCA forming reaction solvent doubles as the good solvent for the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent.



35. (Amended) The crystallization method according to any one of Claims 28 to ~~34~~ 30

wherein the good solvent is a halogenated hydrocarbon, an ether, a nitrile, an ester, a ketone or a mixed solvent thereof.

42. (Amended) The crystallization method according to any one of Claims 28 to ~~41~~ 30

wherein the addition of the aliphatic hydrocarbon solvent to the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)- L-alanine N-carboxylic anhydride in the good solvent is carried out under stirring with a stirring force corresponding to a stirring power requirement of not less than 0.1 kW/m<sup>3</sup>.

44. (Amended) The crystallization method according to any one of Claims 28 to ~~43~~ 30

wherein the addition of the aliphatic hydrocarbon solvent to the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)- L-alanine N-carboxylic anhydride in the good solvent is carried out by preparing a slurry of said N-carboxylic anhydride in advance and adding the aliphatic hydrocarbon solvent sequentially to said slurry.

46. (Amended) The crystallization method according to Claim 44 ~~or 45~~

wherein the preparation of the slurry is carried out by sequential addition of the aliphatic hydrocarbon solvent to the solution of said N-carboxylic anhydride in the good solvent and/or by addition of a crystal of said N-carboxylic anhydride to the solution of said N-carboxylic anhydride in the good solvent.

48. (Amended) The crystallization method according to any one of Claims 28 to ~~47~~ 30 wherein the weight ratio of the good solvent to the aliphatic hydrocarbon solvent is 0.001 to 1 at completion of the addition.

50. (Amended) The crystallization method according to any one of Claims 28 to ~~49~~ 30 wherein an amount of a precipitated crystal is increased by adjusting a liquid temperature to -30 to 25 following completion of the addition.

51. (Amended) The crystallization method according to any one of Claims 28 to ~~50~~ 30 wherein the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent is  
an NCA forming reaction solution obtained by reacting N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine with N,N'-carbonyldiimidazole or phosgene or  
a solution obtained by subjecting the reaction solution to concentration or solvent exchange.

53. (Amended) The crystallization method according to Claim 51 ~~or 52~~ wherein an NCA forming reaction solvent doubles as the good solvent for the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent.